UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DMITRY GABRILOVICH, DAVID CARBONE, SUNIL CHADA and ABNER MHASHILKAR

Appeal No. 2004-1724
Application No. 09/526,320

HEARD: January 25, 2005

ELLIS, ADAMS and GRIMES, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 1-4, 11, 15-22, 24, 26-31 and 33-37, all the claims pending in the application. Claims 5-10, 12-14, 23, 25, 32 and 38-135 have been canceled.

We note that in response to an election of species requirement, the appellants elected to pursue the species of "tumor suppressor genes" as the "self gene."

We further note that the appellants have stated that the claims stand or fall together. Brief, p. 6. During oral argument at the hearing on January 25, 2005, counsel for the appellants stated that in view of the election of species, the claims stand of fall with claim 2. We disagree. We direct attention to claim 3 which better sets forth the elected subject matter. However, both the appellants and the examiner appear to have ignored this election and have considered the issues as they apply not to the subgenus (tumor suppressor genes), but to the species, p53, set forth in claim 11. Accordingly, for purposes of this appeal, we have considered p53 as being representative of the elected species. Claims 1-4 and 11 are illustrative of the subject matter on appeal and read as follows:

1. A method for treating a human subject having or suspected of having cancer or precancerous disease comprising the steps of:

   (i) identifying a subject having or suspected of having cancer or pre-cancerous disease characterized by alteration or increased expression of a self gene product in at least some of the cancer or pre-cancerous cells in said subject; and

   (ii) intradermally administering to said subject an expression construct in an adenovirus particle comprising a self gene under the control of a promoter operable in eukaryotic dendritic cells, wherein the dendritic cells are infected by said construct,

   whereby said self gene product is expressed by dendritic cells and presented to immune effector cells, thereby stimulating an anti-self gene product response.

2. The method of claim 1, wherein said self-gene product is an oncogene.

3. The method of claim 2, wherein said oncogene is selected from the group consisting of tumor suppressors, tumor associated genes, growth factors, growth-factor receptors, signal transducers, hormones, cell cycle regulators, nuclear factors, transcription factors and apoptic factors.

4. The method of claim 3, wherein said tumor suppressor is selected from the group consisting of Rb, p53, p16, p19, p21, p73, DCC, APC, NF-1, NF-2, PTEN, FHIT, C-CAM, E-cadherin, MEN-I, MEN-II, ZAC1, VHL, FCC, MCC, PMS1, PMS2, MLH-1, MSH-2, DPC4, BRCA1, BRCA2 and WT-1.

11. The method of claim 4, wherein said tumor suppressor product is p53.

The examiner relies on the following references for support:

Deonarain et al. (Deonarain), "Ligand-targeted receptor-mediated vectors for gene delivery," Exp. Opin. Ther. Patents, vol. 8, pp. 53-69 (1998).

Hurpin et al. (Hurpin), "The mode of presentation and route of administration are critical for the induction of immune responses to p53 and antitumor immunity," Vaccine, vol. 16, pp. 208-215 (1998).

Marshall, "Gene therapy's growing pains," Science, vol. 269, pp. 1050-55 (1995).

Miller et al. (Miller), "Targeted vectors for gene therapy," The FASEB Journal, vol. 9, pp. 190-199 (1995).

Orkin et al. (Orkin), "Report and recommendations of the panel to assess the NIH investment in research on gene therapy," pp. 1-39 (December 7, 1995).

Restifo et al. (Restifo), "Molecular mechanisms used by tumors to escape immune recognition: Immunogenetherapy and the cell biology of major histocompatibility complex class 1," Journal of Immunotherapy, vol. 14, pp. 182-190 (1993).

Verma et al. (Verma) "Gene therapy- promises, problems and prospects," Nature, vol. 389, pp. 239-242 (1997).

Vogelstein et al. (Vogelstein), "The multistep nature of cancer," Trends in Genetics, vol. 9, pp. 138-141 (1993).

The references relied upon by the appellants are:[1]

Gilbert et al. (Gilbert), "Enhanced CD8 T cell immunogenicity and protective efficacy in a mouse malaria model using a recombinant adenoviral vaccine in heterologous prime-boost immunisation regimes," Vaccine, vol. 20, pp. 1039-1045 (2002).

Kaiserlian et al. (Kaiserlian), "Epicutaneous and transcutaneous immunization using DNA or proteins," Eur. J. Dermatol., vol. 9, pp. 169-76 (1999).

Claims 1-4, 11, 15-22, 24, 26-31 and 33-37 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

We have carefully reviewed the respective positions of both the appellants and examiner and find ourselves in substantial agreement with that of the examiner. Accordingly, we affirm.

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[1] We note that the appellants have attached two exhibits consisting of two publications dated 1998 and May, 2003, to the reply brief. To that end, attention is directed to 37 C.F.R. § 1.195(2004) which states that after appeal any new evidence "will not be admitted without a showing of good and sufficient reasons why they were not earlier presented." (Attention is further directed to new rule 37 C.F.R. § 41.41(a)(2)). Given the dates of the publications, we find that the appellants' argument that they (the publications) were not called to their attention until after receipt of the examiner's Answer does not constitute a showing of good and sufficient reason. Accordingly, we have not considered the new arguments and references provided with the appellants' reply brief.

Background

The specification discloses that cancer in humans is the result of an imbalance between either cell proliferation or cell death. Specification, p. 2. Cell proliferation and death are said to be regulated by proto-oncogenes. Id. Genetic rearrangements or mutations of proto-oncogenes are said to result in the conversion of these genes into cancer-causing oncogenes. Id. Relevant to the claims before us are those proto-oncogenes which are said to encode proteins that inhibit cellular proliferation; viz., p53. Id. A point mutation in the p53 gene is said to result in the loss of wild type p53 function and the acquisition of a tumor promoter function. Id., p. 3. Thus, the presence of tumor suppressors like p53 are said to be essential for the maintenance of a non-tumorigenic phenotype in cells. Id., p. 4. According to the specification, "approximately 50% of all cancers have been found to be associated with mutations of the p53 gene, which result in the loss of p53 tumor suppressor properties." Id.

Also relevant to the claimed invention are dendritic cells. These are specialized antigen-presenting cells which elicit T cell-mediated immune responses. Steinman, "The Dendritic Cell System and Its Role in Immunogenicity," Annu. Rev. Immunol., vol. 9, pp. 271-96 (1991) (of record). Dendritic cells are said to elicit both CD4+ helper cells and CD8+ killer cells, in vivo.

The conventional types of cancer treatment today are surgery, radiation therapy and chemotherapy. Specification, p. 3. The present invention is said to be directed to a

method of treating cancer in humans which involves immunotherapy. Specifically, as indicated by the claims above, the present invention is directed to a method of treating cancer in humans which involves the construction of an adenovirus expression vector comprising (i) a promoter which is functional in dendritic cells; and (ii) a nucleotide sequence encoding a tumor suppressor gene such as p53.

Discussion

As a preliminary matter we point out that any analysis of the claims should begin with a determination of whether they satisfy the requirements of the second paragraph of 35 U.S.C. § 112. In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). It is erroneous to analyze claims based on "speculation as to the meaning of terms employed and assumptions as to the scope of the claims." In re Steele, 305 F.2d 859, 862, 134 USPQ 292, 295 (CCPA 1962). In our view, the claims before us are problematic in that they are somewhat indefinite. However, we find that both the examiner and the appellants have interpreted the claims as being directed, inter alia, to the intradermal administration of an adenovirus particle comprising a tumor suppressor gene (see, subsection (ii)), viz., p53, into a human subject. Said particle is then said to transduce dendritic cells in vivo (in the skin of the human subject), express the tumor suppressor gene product in said dendritic cells, and stimulate an anti-tumor suppressor gene product or, in this case an anti-p53, response in said human. The appellants and the examiner

have interpreted the claims in the same manner and the appellants have indicated that their invention involves the aforementioned sequence of events. Accordingly, in order not to unnecessarily prolong prosecution, we have considered the claims as being directed to a method wherein dendritic cells are transduced in vivo with an adenovirus particle encoding p53. However, we direct attention to our comments below in the "Other Issues" section.

Turning to the rejection, we find that the examiner points out that the specification discloses (i) the construction of an adenovirus expression vector encoding the tumor suppressor gene product p53 (under the control of the CMV I/E promoter) and the in vitro transduction of dendritic cells with said vector; (ii) the intravenous, subcutaneous or intraperitoneal administration of the transduced dendritic cells into mice; and (iii) the inhibition of p53-positive tumors in mice receiving an intravenous administration of the in vitro-transduced dendritic cells (DC) containing the adenovirus/p53 expression vector. Answer, pp. 7-8.

The examiner argues that there is no correlation between the aforementioned specification disclosure and the claimed method of intradermally administering an adenovirus/p53 expression vector into a human which then must transduce dendritic cells present in said human. Id., p. 8. According to the examiner, an adenovirus construct administered to a human will be subject to numerous physiological conditions which will affect its ability to transduce dendritic cells such as "the rate of clearance of the vector from

the injection site, the tropism of the vector for the target cell, the rate of cell transduction under physiological conditions and the presence of any existing immune responses to the virus itself." Id.

The examiner further argues that the treatment of a human cancer is a complex process given that (i) there are many different types and number of mutations present with any particular tumor; (ii) cancer cells are capable of evading host immune responses by numerous mechanisms which could prevent their recognition by the tumor-specific cytotoxic T cells the claimed method is said to elicit; and (iii) humans do not generally mount an immune response against self antigens (a phenomenon known as immune tolerance). Answer, pp. 9-10.

The examiner still further argues that the claimed method is directed to a method of gene therapy and at the time the application was filed (March 15, 1999), those skilled in the art considered the efficiency and efficacy of these methods to be unpredictable. Answer, p. 11. The examiner relies on several publications (Verma, Marshall, Orkin, Deonarain and Miller), for support. Id., p. 12. Moreover, the examiner points out that the prior art teaches that the intradermal injection of a virus encoding the p53 tumor suppressor gene does not result in an anti-p53 immune response in mice. Answer, pp. 12-13. According to the examiner, Hurpin discloses that the CTL response in mice following an intradermal administration of a vaccinia virus/p53 expression construct was lower than the background response obtained from immunization of the vector alone. Id., p. 13.

Thus, the examiner contends that given the lack of any working examples or guidance as to the targeting of the adenovirus/p53 expression constructs to dendritic cells in vivo, and the unpredictable nature of gene therapy, the teachings of the specification would not have enabled one skilled in the art to make and use the claimed method.

In response, the appellants argue that the examiner has only relied on publications which address the issue of gene therapy generally; whereas, their invention is directed to the priming of dendritic cells which in turn stimulate an immune response in the human subject. Brief, p. 8. Thus, high transduction efficiency is not necessary for therapeutic efficacy in treating cancer. Id. The appellants rely on Kaiserlian for support.

The appellants further argue that Verma does not address the priming of dendritic cells, and that the publication is directed to problems associated with gene delivery and transient expression. Brief, p. 8. The appellants still further argue that Marshall and Orkin, teach problems which occur with therapies that require the "replacement of defective genes, long term expression of genes and/or the transfection of large numbers of cells in vivo." Id., p. 9. The appellants contend that these publications are a testament to the fact that gene therapy works, but that the conditions have yet to be fully optimized. Id. The appellants point out that to satisfy the enablement requirement, a specification need not provide teachings which render the invention commercially applicable or completely optimized. Id.

With respect to the Hurpin publication, the appellants argue that the publication is directed to problems generating a CTL response when a different virus/promoter/p53 construct is intradermally injected into mice. Brief, p. 9. The appellants contend that because Hurpin does not address the issue of using different viral vectors and different promoters and their propensity to transduce dendritic cells, the examiner is only speculating that a similar response would be seen using adenovirus to immunize the mice. Id. Moreover, the appellants argue, Hurpin does not test the immunized mice for the ability to protect against tumor challenge. Id.

With respect to the ability of an adenovirus construct to stimulate an immune response in an immunized animal, the appellants point to the teachings of Gilbert that the intradermal or muscular injection of an adenovirus encoding the CS gene of Plasmodium berghei (a rodent malaria) induced a strong CD8(+) T cell response in mice. Brief, p. 10.

As to the teachings of Vogelstein and Restifo, the appellants argue that the publications do not rebut the results disclosed in the specification examples with respect to the identification of other self genes which are up-regulated or have altered expression in cancer cells. Brief, p. 11. In addition, the appellants further argue that because dendritic cells are responsible for the presentation of the epitope, any function of a particular polypeptide is irrelevant. Id. Thus, the appellants contend "that the heterogeneity of the tumor suppressor oncogene mutations in a particular tumor is irrelevant due to the guidance provided in identifying at least one tumor suppressor or oncogene product.

Furthermore, the various mechanisms by which tumor cells evade an innate immune response has no bearing on a stimulated immune response as provided in the examples provided in the instant specification." Id., pp. 11-12.

The appellants' arguments are unpersuasive.

We find the appellants' and examiner's arguments with respect to the teachings of the Hurpin (relied upon by the examiner) and Gilbert (relied upon by the appellants) publications to be dispositive of the enablement issue.

As pointed out by the examiner, Hurpin teaches that the intradermal administration of a vaccina virus (specifically, an attenuated canary pox virus) vector comprising a full-length, wild-type human p53 nucleotide sequence does not induce a CD8+ CTL (cytotoxic T lymphocyte) response in mice. Hurpin discloses that the intradermal route of administration has been classically used for immunization with pox virus vectors and that "[t]he attenuated canary pox virus ALVAC has been shown in a number of clinical studies to be well tolerated and capable of inducing both humoral and cellular responses." Hurpin, p. 208, col. 1; p. 210, col. 2, para. 1. However, the intradermal administration of the vaccina virus/p53 expression construct resulted in a lower immune response in the mice than the control virus. See Figure 1(a). In contrast, intravenous administration of said expression construct induced the production of CD8+ CTLs capable of lysing tumor cells. Hurpin concludes that the route of administration of

the expression vector is critical for the induction of an optimal immune response. Hurpin, p. 213, col. 1.

Given Hurpin's teachings that (i) the canary pox virus is known to induce a humoral and cellular immune response when intradermally administered to a subject; and (ii) the vaccina virus/p53 expression construct elicits a protective immune response to tumors when administered intravenously, we find the appellants' argument that the poor results obtained when said construct was administered intradermally were due to the vector/promoter construct, lacks merit. Rather, we find that Hurpin supports the examiner's position that the results disclosed in the specification examples which describe intravenously administering dendritic cells already transformed with a viral expression vector comprising a nucleotide sequence encoding p53 are not indicative of the results which will be obtained when an adenovirus/p53 expression construct is administered intradermally in a human cancer patient. That is, Hurpin provides evidence that the specification would not have enabled one skilled in the art to "make and use" the claimed method of treating human cancer patients by intradermally administering an adenovirus comprising a nucleotide sequence encoding p53, at the time the application was filed.

Turning to the Gilbert publication relied upon by the appellants, we are not persuaded that its teachings with respect to mounting an immune response to a rodent malaria antigen (the CS (circumsporozoite)) antigen on the surface of the sporozoite stage of the parasite life cycle) which is present in the blood stream for a short period of time

(less than one hour) before entering a liver cell, is analogous to the claimed method of treating tumors in humans which reasonably appears to require a prolonged immune response to a disease having a totally different pathology. Even if we assume, arguendo, that the disease states are comparable, we do not find that the teachings of Gilbert show that one skilled in the art would have been enabled to make and use the claimed invention. Our reasons follow.

First and foremost, we find that the method disclosed by Gilbert is not the same as the claimed method. To that end, we point out that Gilbert teaches the intradermal administration in mice of an adenovirus/CS gene expression construct to prime a CD8+ CTL response. Fourteen days later, the mice were boosted with a vaccinia virus/p53 expression construct. Gilbert reports that it was the combination of adenovirus priming and boosting with the heterologous vaccina virus expression construct that resulted in "extremely high numbers of peptide specific CD8+ T cells." Gilbert, p. 1041, col. 2, first complete para. Intradermal priming (administration) of adenovirus followed by boosting, intradermally, with the vaccina virus is said to completely protect immunized mice. Id., p. 1042, col. 2; Table 1. Gilbert further reports that "[h]eterologous priming and boosting is clearly more effective than using the same vaccine repeatedly." Id., p. 1041, col. 2., para. 2. We point out that two sequential administrations of the adenovirus/p53 expression construct did not result in protection. Id., p. 1043, col. 1, para. 1; Table 1.

Contrary to the appellants' arguments, the claimed method is not directed to the priming of the human subject with the adenovirus/p53 construct followed by a boost with a heterologous vector encoding p53. Rather, we find that one skilled in the art would have understood from the method described in the claims that one intradermal administration of the adenovirus/p53 expression construct could be used to treat cancer in humans. The results reported by Gilbert indicate that this is not the case. Moreover, the teachings of Gilbert suggest that multiple immunizations with the claimed adenovirus/p53 construct would not elicit an anti-p53 response in a human subject suspected of having cancer. Thus, we agree with the examiner that given the unpredictable nature of the invention, the teachings of the specification with respect to the intravenous, intramuscular and subcutaneous administration of an adenovirus/p53 expression construct (see, pages 71 and 72) would not have enabled one skilled in the art to "make and use" the claimed method, at the time the application was filed.

With respect to the teachings of Kaiserlian, we find the appellants' arguments concerning this publication to be misplaced. Referring to the section relied upon by the appellants (p. 171, col. 1, last para.), we find that Kaiserlian discloses DNA vaccine trials. Kaiserlian describes DNA vaccination as involving the delivery of DNA in one of three forms: (1) naked DNA; (2) plasmid DNA coated onto gold particles; and (3) plasmid DNA encapsulated into inert vectors such as biodegradable microspheres. Kaiserlian, p. 170, para. bridging cols. 1-2. With respect to the administration of an adenovirus construct, the

examiner points out that Kaiserlian discloses a method which involves first tape-stripping the corneal layer of the skin followed by application of the adenovirus by occlusive technique (p. 174, col. 1, last para.). Answer, p. 20. Since the claimed method is directed to the intradermal administration of an adenovirus/p53 expression construct, we find that neither the section of the publication relied upon by the appellants, nor the teachings with respect to adenovirus constructs, address a limitation present in the claims.

We agree with the appellants that the gene therapy references relied upon by the examiner do not teach the priming of dendritic cells, but as discussed above, the claimed method has no priming step. Thus, we find that the appellants' arguments in this regard do not address a limitation present in the claims. Accordingly, we find no error with the examiner's application of said references.

We also agree with the appellants that the specification need not provide teachings which render the invention commercially applicable or completely optimized. However, in view of the method set forth in the claims, the specification must provide teachings which would have enabled one skilled in the art to stimulate an anti-self (anti-p53) immune response sufficient to treat a human subject having or suspected of having cancer. We find that the problems with gene therapy raised by the examiner to be appropriately directed to the level of immune response required by the claims.

Finally, we note the appellants' contention that there is no requirement or limitation in the claimed method for specifically targeting a dendritic cell (Brief, p. 10). We

find this argument to be one of semantics. During oral hearing counsel for the appellants acknowledged that if dendritic cells are not transduced in vivo, and p53 is not expressed by said cells, the claimed method does not work. Thus, we find no error in the examiner's reliance of Verma, Marshall, Orkin and Deonarain.

Other Issues

As discussed above, analysis of the claims should begin with the determination of whether the claims satisfy the requirements of the second paragraph of § 112. In re Moore, 439 F.2d at 1235, 169 USPQ at 238. In Moore, the court stated:

> . . . it should be realized that when the first paragraph speaks of "the invention", it can only be referring to that invention which the applicant wishes to have protected by the patent grant, i.e, the claimed invention. For this reason the claims must be analyzed first in order to determine exactly what subject matter they encompass. The subject matter there set out must be presumed, in the absence of evidence to the contrary, to be that "which the applicant regards as his invention."
>
> This first inquiry therefore is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. It is here where the definiteness of the language employed must be analyzed- not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.

Accordingly, in the event of further prosecution of the present application, the examiner may wish to consider whether the claims satisfy the requirements of 35 U.S.C. § 112, second paragraph.

To that end, the examiner should consider whether claim 1 is vague and indefinite in the recitation of "the dendritic cells" in line 8. We point out that there is no antecedent basis for this phrase.

With respect to claim 2, the examiner should consider whether the claims are vague and confusing in the recitation of a "self gene product" which is an "oncogene." A gene product refers to a protein which is encoded by a gene. An oncogene is a type of gene; i.e., it is a DNA sequence. It appears the appellants intend either a self gene which is an oncogene or a self gene product which is an oncogenic protein.

In view of the foregoing, the decision of the examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. 1.136(a).

AFFIRMED

JOAN ELLIS Administrative Patent Judge	) BOARD OF PATENT
DONALD E. ADAMS Administrative Patent Judge	) APPEALS AND) INTERFERENCE
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